http://dx.doi.org/10.5012/bkcs.2012.33.1.123

A Green and Highly Efficient Solvent-free Synthesis of Novel Calicx[4]resorcinarene Derivatives Using Tungstate Sulfuric Acid

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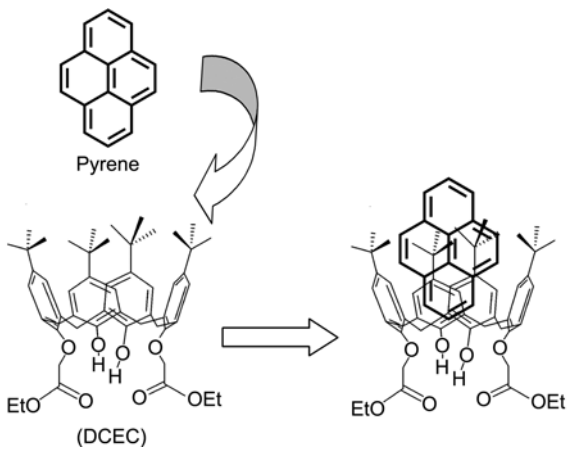
Received September 19, 2011, Accepted November 7, 2011

A facile and simple procedure for the synthesis of novel and known calix[4]resorcinarene derivatives were developed *via* a reaction of arylaldehydes with resorcinol in the presence of catalytic amounts of tungstate sulfuric acid (TSA) under solvent-free conditions. This eco-friendly method has many appealing attributes, such as excellent yields, short reactions times, use of safe and recoverable catalyst, and simple work-up procedures. TSA was characterized by powdered X-ray diffraction (XRD), X-ray fluorescence (XRF) and FT-IR spectroscopy.

Key Words : Calix[4]resorcinarene, Arylaldehyde, Resorcinol, Tungstate sulfuric acid

Introduction

Aromatic macrocyclic chemistry has attracted the attention of many chemists in recent years.[1] calix[4]resorcinarenes, a subclass of calixarenes, are large cyclic tetramers which have found applications, as macrocyclic receptors,[2] dendrimers in biological systems,[3] nanoparticles,[4] nano-capsule,[5] supramolecular tectons,[6] optical chemosensors,[7] host molecules or host-guest complexes,[8,9] components in liquid crystals,[10] photoresists,[11] selective membranes,[12] HPLC stationary phases,[13] surface reforming agents,[14] ion channel mimics,[15] and metal ion extraction agents.[16] For example, in a valuable study by Sanchez-Cortes, Leyton, and co-workers entitled "selective molecular recognition of polycyclic aromatic hydrocarbons (PAHs) on calix[4]arene-functionalized Ag nanoparticles by surface-enhanced raman scattering" the 25,27-dicarboethoxy-26,28-dihydroxy-*p*-*tert*-butylcalix[4]arene host molecule (DCEC) displays analytical selectivity to the polycyclic aromatic hydrocarbon guest systems bearing four benzene rings, mainly pyrene (Scheme 1). They have deduced a host-guest interaction mechanism through π-π stacking between the aromatic systems of DCEC and PAHs.[17]

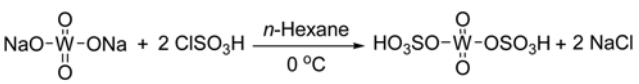


Scheme 1. Host/guest complex formation on the surface.

It should be noted that the synthesis of calix[4] resorcinarenes was first reported in the late 19th century by Bayer based on the concentrated sulfuric acid catalyzed cyclocondensation of benzaldehyde and resorcinol.[18,19] Although different synthetic routes have been used for the synthesis of calix[4]resorcinarene derivatives by employing some Lewis acid catalyst, however, some of these strategies suffer from disadvantages such as low product yield, cumbersome isolation of the product and long reaction time. In the past few years, we have been involved in a program directed towards developing simple, novel, and facile methods for the preparation of organic compounds using various catalysts and readily available starting materials.[20-22] Also, in a recent paper, we reported synthesis of aza-polycyclic aromatic compounds such as novel phenazines and quinoxalines using molybdate sulfuric acid.[23] This stimulated our interest for further studies on the chemistry of catalysts.

Results and Discussion

The challenge in chemistry to develop the practical methods, reaction media, conditions and/or the use of materials based on the idea of green chemistry is one of the important issues in the scientific community. However, the concept of "Green Chemistry" has emerged as one of the guiding principles of the environmentally organic synthesis. Recently silica sulfuric acid and Nafion-H® [24,25] have been used for a wide variety of reactions.[26,27] Accordingly, we found that anhydrous sodium tungstate reacts with chlorosulfonic acid (1:2 mole ratio) to give tungstate sulfuric acid (TSA **1**). The reaction is easy and clean and performed there is no gas



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Scheme 2. Preparation of tungstate sulfuric acid (TSA **1**).

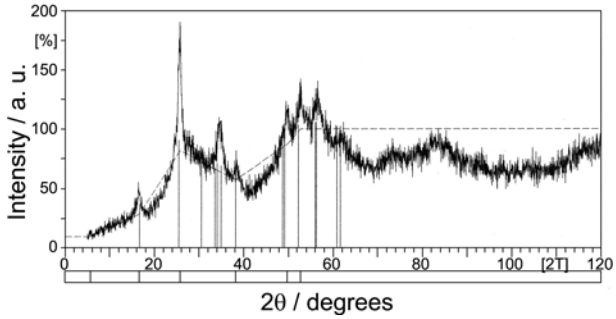


Figure 1. The powder X-Ray Diffraction pattern of the tungstate sulfuric acid (TSA **1**).

Table 1. XRF data of TSA **1**

Compound	Concentration (%W/W)
WO_4	19.49
SO_3	0.317
Na_2O	0.190
Cl	0.056
CuO	0.023
Fe_2O_3	0.015
CaO	0.014
LOI[a]	79.82
Total	99.93

[a]Loss on Ignition.

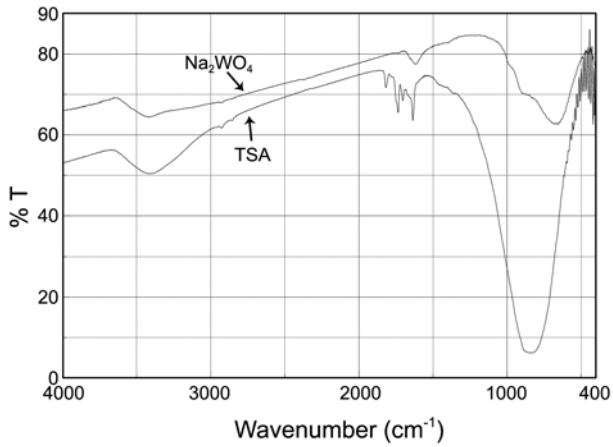
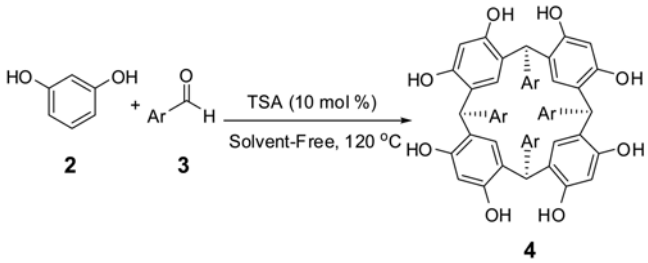


Figure 2. FT-IR spectra of TSA **1** and sodium tungstate.



Scheme 3. Synthesis of calix[4]resorcinarenes using TSA **1**.

production during the reaction (Scheme 2).

Figure 1 shows the XRD patterns of tungstate sulfuric acid (TSA **1**). It was reported that high degree mixing of W-S in chlorosulfonic acid often led to the absence of XRD pattern for anhydrous sodium tungstate.

The broad peak around 25.7° (2θ) (θ is the Braggs angle) from the smaller inset could be attributed to insertion of W into the framework of chlorosulfonic acid. The XRF data of tungstate sulfuric acid (TSA **1**) indicates the presence of WO_4 and SO_3 in this catalyst (Table 1).

The FT-IR spectra of anhydrous sodium tungstate and tungstate sulfuric acid (TSA **1**) are shown in Figure 2. The spectrum of tungstate sulfuric acid (TSA **1**) shows the characteristic bonds of anhydrous sodium tungstate and chlorosulfonic acid. The absorption in 3406, 1820, 1725, 1702, 1620, 1290, 1060, 1005 and 860 cm^{-1} in the catalyst spectrum reveal both bonds in anhydrous sodium tungstate and $-OSO_3H$ group.

In this work, we describe a simple and green strategy based on the condensation of resorcinol **2** with arylaldehyde **3** using TSA **1** as a powerful, recyclable and safe catalyst under solvent-free conditions for the preparation of novel and known calix[4]resorcinarene derivatives **4** (Scheme 3).

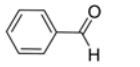
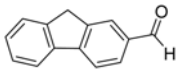
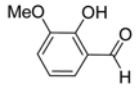
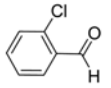
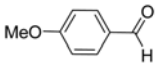
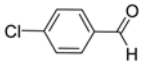
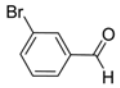
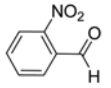
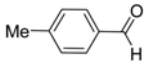
The need to implement green chemistry principles (e.g. safer solvents, less hazardous chemical synthesis, atom economy and catalysis) is a driving force towards the avoidance of the use of toxic organic solvents. A solvent-free or solid state reaction obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour. However, interest in the environmental control of chemical processes has increased remarkably during three decades ago as a response to public concern about the use of hazardous chemicals. Therefore, to improve the effectiveness of this method in preventing chemical waste, it is important to investigate optimal reaction conditions.

To determine the suitable reaction conditions, the reaction of benzaldehyde with resorcinol was taken as a model reaction. At first, we found that in the absence of TSA **1**, the reaction not completed in long reaction times (650 min). After examining the various amounts of TSA **1** at 120 °C, it was found that the reaction can be efficiently carried out by adding 10 mol % of the catalyst under solvent-free conditions in a short time span of 25 min. The use of excessive amounts of the catalyst does not increase the yield and reaction rate. According to Table 2, under the optimized reaction conditions, a number of aromatic aldehydes were allowed to undergo reaction with resorcinol in a molar ratio of 1:1 with catalyst affording calix[4]resorcinarenes **4a-4i** in good to excellent yields.

In an important variation, as can be seen in Scheme 4 (Table 2, Entry 2), the macrocyclic compound **4b** as a calix [4]resorcinarene containing a polycyclic aromatic hydrocarbon substituent such as 9*H*-fluorene were synthesized.

Figure 3 is a one-dimensional ^{1}H-NMR spectrum of compound **4b** which shows distinct resonances in agreement with the proposed structure. Obviously, the ^{1}H NMR spectrum of **4b** exhibit two singlet as protons of methylene group of fullereneyl (δ = 3.50 ppm), and proton of methyne group

Table 2. Synthesis of calix[4]resorcinarene derivatives catalyzed with TSA **1** at 120 ºC under solvent-free conditions

Entry	Product	Ar	Time (min)	Yield (%)[a]	mp ºC (decompose)
1	**4a**		25	90	297
2	**4b**		80	85	298
3	**4c**		60	85	264
4	**4d**		45	90	270
5	**4e**		25	80	262
6	**4f**		30	85	264
7	**4g**		30	95	269
8	**4h**		50	80	225
9	**4i**		45	78	240

[a]Isolated yields.

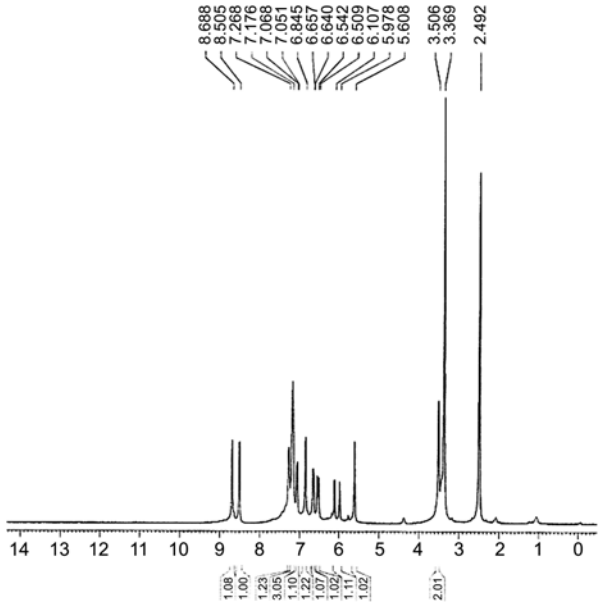
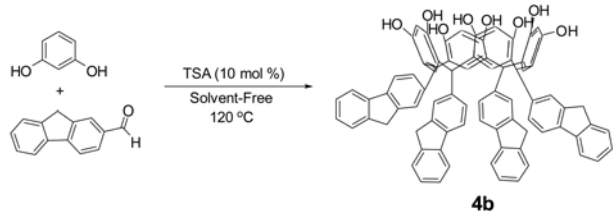


Figure 3. One-dimensional ^{1}H-NMR spectrum of **4b**.

(δ = 5.60 ppm). Seven signals (δ = 5.97-7.26 ppm) correspond to the aromatic protons. Also, the resonance of proton of two OH groups in the ^{1}H NMR spectrum of **4b** appeared at δ = 8.50 and 8.68 ppm as two singlet signal.

Not only the ecological profile (through helping to decrease hazardous industrial waste), but also the economic profile (through the elimination of expensive organic solvent) is further improved if the catalyst is recyclable and reaction conditions are solvent-free. In this process, as indicated in Figure 4, the recycled catalyst was used for four cycles during which a little appreciable loss was observed in the catalytic activities.



Scheme 4. Synthesis of 2-fluorenyl-phenyl-calix[4]resorcinarene **4b**.

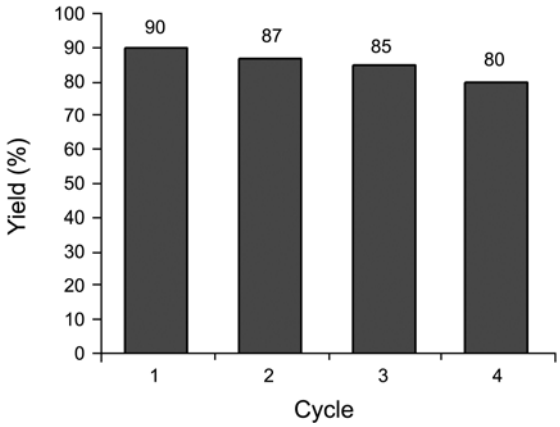


Figure 4. Recyclability of TSA**1** as catalyst for the synthesis of 4a on the condensation of aldehydes (1 mmol), resorcinol (1 mmol) at 120 ºC under solvent-free conditions. Reaction time = 25-40 min.

Experimental

General. The chemicals were purchased from Merck, Fluka, and Aldrich companies. The reactions were monitored by TLC (silica-gel 60 F_{254}, *n*-hexane: ethyl acetate). IR spectra were recorded on a FT-IR Shimadzu-470. Spectrometer and the ^{1}H and ^{13}C NMR spectra were obtained with a Bruker-Instrument DPX-400 and 500 MHz Avance 2 model. X-Ray Diffraction (XRD) pattern was obtained by Philips X Pert Pro X diffractometer operated with a Ni-filtered Cu Kα radiation source. X-Ray Fluorescence (XRF) spectroscopy was recorded by X-Ray Fluorescence Analyzer, Bruker, S_4 Pioneer, Germany. Mass spectra were recorded on Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The varioEl CHN Isfahan Iindustrial University was used for elemental analysis.

Preparation of Catalyst. At first, 25 mL of dry *n*-Hexane was taken in a 100 mL round bottom flask, equipped with ice bath and overhead stirrer, and 0.588 g (2 mmol) of anhydrous sodium tungstate was added to the flask, then 0.266 mL (4 mmol) of chlorosulfonic acid was added dropwise to

the flask for 30 min. This solution was stirred for 1.5 h. Afterwards the reaction mixture was gradually poured into 25 mL of chilled distilled water with agitation. The yellowish solid which separated out was filtered. Then catalyst was washed with distilled water for five times till the filtrate showed negative test for chloride ion, and dried at 120 °C for 5 h. The catalyst was obtained in 98% yield as a yellowish solid, which decomposed at 285 °C.

Preparation of Calix[4]resorcinarene Derivatives 4. A mixture of resorcinol 1 (1 mmol), aryl aldehyde 2 (1 mmol), and TSA (10 mol %) was stirred and heated at 120 °C in a preheated oil bath for appropriate time (Table 2). After completion of the reaction as indicated by TLC (ethyl acetate/*n*-hexan 7:3), the reaction mixture was dissolved in hot methanol, then filtered to separate catalyst and afford pure product **4**. The separated catalyst was washed with diethyl ether, dried at 70 ºC for 45 min, and reused in another reaction.

Spectral Data.

Phenyl-calix[4]resorcinarene (4a). IR (KBr), cm^{-1}: 3400, 3022, 1611, 1510, 1230, 1090; ^{1}H-NMR (400 MHz, DMSO), δ (ppm): 8.93-8.88; (m, 2H), 7.17-5.74 (m, 6H), 5.70 (s, 1H); ^{13}C-NMR (100 MHz), δ (ppm): 156.68, 155.85, 153.42, 146.02, 130.53-125.29 (8c), 106.67, 105.83, 63.27; Anal. Calcd. for $C_{52}H_{40}O_8$: C, 78.77; H, 5.09. Found: C, 77.80; H, 5.51; MS (*m*/*z*: 792).

2-Fluorenyl-phenyl-calix[4]resorcinarene (4b). IR (KBr), cm^{-1}: 3436, 2923, 1613, 1503, 1424, 1191, 1062, 767, 731; ^{1}H-NMR (400 Hz, DMSO), δ (ppm): 8.68 (s, 1H), 8.50 (s, 1H), 7.05-7.17 (s, 4H), 6.50-6.64 (s, 3H), 6.10 (s, 1H), 5.97 (s, 1H), 5.60 (s, 1H), 3.50 (s, 2H); ^{13}C-NMR (125 MHz, DMSO), δ (ppm): 170.16, 153.37, 153.06, 143.79, 143.04, 142.30, 141.57, 138.10, 132.27, 129.46, 128.20, 126.81, 126.29, 126.14, 125.07, 121.92, 121.02, 119.59, 118.46, 102.47, 102.05, 95.87, 42.71, 21.25. Anal. Calcd. for $C_{80}H_{56}O_8$: C, 83.90; H, 4.93. Found: C, 83.02; H, 4.25.

2-Hydroxy-3-methoxy-phenyl-calix[4]resorcinarene (4c). IR (KBr), cm^{-1}: 3474, 2938, 2840, 1640, 1477, 1272, 1062, 778, 728; ^{1}H-NMR (400 Hz, DMSO), δ (ppm): 8.17 (s, 1H), 8.14 (s, 1H), 8.13 (s, 1H), 7.51 (s, 1H), 7.49 (s, 1H), 6.43-6.25 (s, 3H), 6.01 (s, 1H), 5.96 (s, 1H), 5.85 (s, 1H), 3.65 (s, 3H), 3.60 (s, 3H); ^{13}C-NMR (100 MHz), δ (ppm): 153.16, 152.81, 152.72, 152.48, 146.91, 146.65, 143.42, 143.26, 132.81, 131.41, 123.51, 122.83, 122.25, 122.14, 120.26, 119.50, 117.67, 117.45, 108.84, 101.98, 56.28, 35.00, 34.43; Anal. Calcd. for $C_{56}H_{48}O_{16}$: C, 68.85; H, 4.95. Found: C, 67.75; H, 4.10; MS (*m*/*z*: 974.8).

2-Chloro-phenyl-calix[4]resorcinarene (4d). IR (KBr), cm^{-1}: 3446, 2922, 2852, 1617, 1508, 1424, 1272, 1062, 731; ^{1}H-NMR (400 Hz, DMSO), δ (ppm): 8.63 (s, 1H), 8.59 (s, 1H), 8.55 (s, 1H), 6.96-6.88 (s, 4H), 6.12 (s, 1H), 5.96 (s, 1H; ^{13}C-NMR (100 MHz), δ (ppm): 153.59, 153.33, 143.96, 133.74, 130.02, 129.23, 128.85, 126.83, 125.94, 120.39, 118.34, 102.23; Anal. Calcd. for $C_{52}H_{36}Cl_4O_8$: C, 67.11; H, 3.90. Found: C, 67.65; H, 3.22; MS (*m*/*z*: 929.1).

4-Methoxy-phenyl-calix[4]resorcinarene (4e). IR (KBr), cm^{-1}: 3391, 3027, 3001, 1608, 1509, 824; ^{1}H-NMR (400 Hz, DMSO), δ (ppm): 8.34 (s, 2H), 6.54 (s, 4H), 6.33 (s, 1H), 5.85 (s, 1H), 5.28 (s, 1H), 4.07 (s, 3H); ^{13}C-NMR (125 Hz, DMSO): 170.13, 156.90, 152.88, 13818, 130.16, 129.79, 121.17, 122.90, 102.35, 95.84; Anal. Calcd. for $C_{56}H_{48}O_{12}$: C, 73.67; H, 5.30. Found: C, 72.85; H, 5.89; MS (*m*/*z*: 912.4).

4-Chloro-phenyl-calix[4]resorcinarene (4f). IR (KBr), cm^{-1}: 3410, 3036, 2942, 1617, 1487, 1076; ^{1}H-NMR (400 Hz, DMSO), δ (ppm): 8.48 (s, 2H), 6.79 (d, 2H, J = 12 Hz), 6.41 (d, 2H, J = 12 Hz), 5.98 (s, 2H), 5.39 (s, 1H); ^{13}C-NMR (100 MHz), δ (ppm): 154.31, 146.15, 131.88, 131.25, 128.43, 121.46, 103.25, 42.56; Anal. Calcd. for $C_{52}H_{36}Cl_4O_8$: C, 67.11; H, 3.90. Found: C, 66.54; H, 4.14; MS (*m*/*z*: 929.1).

3-Bromo-phenyl-calix[4]resorcinarene (4g). IR (KBr), cm^{-1}: 3445, 2940, 1595, 1488, 1260, 1092, 880, 780, 690; ^{1}H-NMR (400 MHz, DMSO), δ (ppm): 9.12-8.92 (m, 2H), 7.14-6.56 (m, 4H), 6.25-6.02 (m, 2H), 5.67 (s, 1H); ^{13}C-NMR (100 MHz), δ (ppm): 156.63, 155.80, 131.49, 129.93, 128.09, 121.50, 105.92, 102.64; Anal. Calcd. for $C_{52}H_{36}Br_4O_8$: C, 56.34; H, 3.27. Found: C, 55.74; H, 3.32.

2-Nitro-phenyl-calix[4]resorcinarene (4h). IR (KBr), cm^{-1}: 3410, 3080, 2910, 1681, 1605, 1520, 1335, 1150, 730; ^{1}H-NMR (400 MHz, DMSO), δ (ppm): 9.10-8.96 (m, 2H), 7.76-5.96 (m, 6H), 4.76 (s, 1H); ^{13}C-NMR (100 MHz), δ (ppm): 170.20, 157.13, 155.91, 154.07, 150.13, 149.30, 139.45, 132.40-124.23 (8C), 119.94, 106.66, 105.93, 102.69, 67.43; Anal. Calcd. for $C_{52}H_{36}N_4O_{16}$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.78; H, 3.22; N, 4.98; MS (*m*/*z*: 973.1).

4-Methyl-phenyl-calix[4]resorcinarene (4i). IR (KBr), cm^{-1}: 3405, 3010, 2910, 1600, 1505, 1125.840; ^{1}H-NMR (400 MHz, DMSO), δ (ppm): 9.10-8.88 (m, 2H), 7.10-6.20 (m, 6H), 5.67 (s, 1H), 2.19 (s, 3H); ^{13}C-NMR (100 MHz), δ (ppm): 158.91, 156.60, 130.16, 128.99, 128.37, 106.66, 105.81, 102.79, 21.04; Anal. Calcd. for $C_{56}H_{48}O_8$: C, 79.22; H, 5.70. Found: C, 78.35; H, 5.05; MS (*m*/*z*: 854.7).

Conclusion

In summary, a green synthetic route to novel and known calix[4]resorcinarene derivatives using TSA**1** under solvent-free conditions was presented. Using this method not only gives high yield and purity but also is a cheap, speedy, facile, and eco-friendly method throughout the course of the reaction.

Acknowledgments. The authors gratefully acknowledge partial support of this work by the YsoujUniversity, Yasouj, Iran.

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